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ORIGINAL REPORT

Elevated Incidence of Lung Cancer Among HIV-Infected Individuals

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ABSTRACT

Purpose
People with HIV infection in the United States frequently smoke tobacco. We sought to characterize lung cancer incidence among HIV-infected individuals, examine whether cancer risk was related to HIV-induced immunosuppression, and assess whether the high prevalence of smoking explained elevated risk.

Methods
We conducted a retrospective cohort study at an HIV specialty clinic in Baltimore, MD (1989-2003). Incident lung cancers were identified using hospital records. We used negative binomial regression to compare incidence across subgroups defined by demographics, use of highly active antiretroviral therapy (HAART), and HIV markers. Standardized incidence ratios (SIRs) compared incidence with an urban reference population (Detroit, MI). We adjusted SIRs for the effect of smoking, using smoking prevalences estimated from part of the cohort and the general population. 95% CIs and *P* values were two sided.

Results
Thirty-three lung cancers were observed among 5,238 HIV-infected patients (incidence: 170 per 100,000 person-years). Incidence increased with age ($P < .0001$), but did not differ by sex, race, or CD4 count. Incidence tended to increase with calendar year ($P = .09$) and HAART use ($P = .10$), and was inversely related to HIV viral load ($P = .03$), but these associations were attenuated with age adjustment. The SIR was 4.7 (95% CI, 3.2 to 6.5) versus the general population. Twenty-eight lung cancer patients (85%) and 69% of the cohort were smokers. After smoking adjustment, risk remained elevated (SIR, 2.5; 95% CI, 1.6 to 3.5).

Conclusion
Lung cancer risk was substantially elevated in HIV-infected individuals. Incidence was unrelated to HIV-induced immunosuppression. Notably, incidence remained high after adjustment for smoking, suggesting the involvement of additional factors.

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INTRODUCTION

Among people with HIV infection, the widespread use of highly active antiretroviral therapy (HAART) beginning in 1996 has led to dramatic improvements in immune status and reduced AIDS-related morbidity. Of concern, people living with HIV/AIDS in the United States and Europe have disproportionately high rates of tobacco smoking. With prolonged survival of HIV-infected persons, smoking-related diseases, including smoking-related cancers, may become a significant cause of morbidity.

Lung cancer is the leading cause of cancer death in the general US population. It is also the most common non–AIDS-defining cancer in people with HIV infection[1] and is highly lethal in that setting.[2] A number of epidemiologic studies have noted an elevated risk of lung cancer among HIV-infected individuals.[3-9] The degree to which the risk is due to tobacco use has remained uncertain, as most studies have had few or no data on tobacco use among HIV-infected persons.[10] The potential relationship between HIV-induced immunosuppression and lung cancer incidence has also been difficult to clarify.

To better understand the epidemiology of lung cancer in people with HIV/AIDS, we studied a cohort attending a hospital-based outpatient clinic in inner city Baltimore, MD. We sought to characterize the relationship of lung cancer incidence with markers of HIV-related immunosuppression and use of HAART. Additionally, we wanted to determine the degree to which smoking explained the occurrence of lung cancer in this population.

METHODS

The Johns Hopkins Hospital Moore Clinic provides longitudinal care to HIV-infected individuals living in Baltimore. Clinic patients undergo a detailed baseline evaluation, with collection of demographic, behavioral, and clinical data. Decisions regarding antiretroviral therapy are made by individual clinic health care providers, following accepted practice guidelines. HIV disease markers (ie, CD4 counts and beginning in 1996, HIV viral loads) are routinely measured at 3-month intervals, or more frequently if clinically indicated. Since 1989, data from Moore Clinic medical records and hospital sources have been abstracted and entered into an observational database.[11] Registration in this database defines a prospectively followed cohort (ie, Moore Clinic cohort). For the present study, data were complete through 2003. The Johns Hopkins Hospital institutional review board approved this study.

Lung cancer in Moore Clinic cohort subjects was identified through two mechanisms. First, cases were noted during data abstraction as part of routine follow-up. The abstraction process obtains clinical information from both Johns Hopkins–affiliated hospitals and outside hospitals and medical facilities. Although we sought lung cancer cases from other institutions in this way, all identified cases were actually treated at Johns Hopkins Hospital. Second, we matched the Moore Clinic database with a database of lung cancer patients treated at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Hospital (N = 4,582 records for the period from 1989 to 2003). Because we were interested in estimating lung cancer incidence, we included only lung cancer cases for which patients were followed in the Moore Clinic before cancer diagnosis (four prevalent cases were excluded). All lung cancer cases were pathologically confirmed.

For each calendar year of follow-up, cohort subjects were classified as of the start (ie, January 1) of that year according to age, HIV treatment prescribed by their primary provider (HAART *v* no HAART, beginning in 1996), and most recent HIV disease markers (CD4 count, nadir CD4 count, HIV viral load). For applying year-specific rates obtained from cancer registries (see next paragraph) and to create periods with somewhat equal amounts of follow-up time, before analysis we divided the follow-up time within the cohort according to calendar years (1989 to 1994, 1995 to 1999, and 2000 to 2003). We calculated lung cancer incidence as cases per 100,000 person-years and compared lung cancer incidence across subgroups using negative binomial regression. All 95% CIs and *P* values were two-sided.

We used standardized incidence ratios (SIRs) to determine whether lung cancer incidence was elevated in our cohort. The SIR is defined as the ratio of observed lung cancers to the number expected based on general population rates. For general population rates, we used sex-, age-, race-, and calendar year–specific rates from the National Cancer Institute Survival, Epidemiology and End Results (SEER) registry program (public use data available at http://seer.cancer.gov). Rates were derived from all SEER sites combined where indicated, but for most analyses, we used data only from Detroit, MI, SEER. We chose Detroit as our reference population because this site is a medium-sized city resembling Baltimore and has the highest lung cancer incidence among major SEER registries (SEER does not cover Baltimore itself). Expected counts were calculated for lung cancer overall, as well as for specific histologic types, using a scheme modified from Jemal et al.[12] We report exact two-sided 95% CIs for SIRs, and compared SIRs across cohort subgroups using Poisson regression.

Data on tobacco use for lung cancer cases were retrieved from the Sidney Kimmel Comprehensive Cancer Center database. However, data on tobacco use were available for only approximately one third of the Moore Clinic cohort (specifically, those patients entering the cohort in 1999 or thereafter). We therefore could not examine lung cancer incidence in the cohort according to smoking status, nor directly adjust for the effects of smoking. Rather, we used an indirect method for adjusting the SIRs for the effect of smoking. As described in more detail elsewhere[13] and in the Statistical Appendix (available online only), we obtained smoking-adjusted SIRs by dividing the observed SIRs by a bias factor,

$$\textit{bias factor} = (1 - p_{\text{smoker, exp}} + \text{RR}_{\text{smoke}} \times p_{\text{smoker, exp}})/(1 - p_{\text{smoker, nonexp}} + \text{RR}_{\text{smoke}} \times p_{\text{smoker, nonexp}})$$

where $p_{\text{smoker, exp}}$ and $p_{\text{smoker, nonexp}}$ are the prevalence of smoking in the HIV-infected cohort (exposed) and in the general population (nonexposed), respectively, and RR_{smoke} is the relative risk (RR) for lung cancer conveyed by smoking. We used smoking data for cohort patients entering in 1999 or after to estimate $p_{\text{smoker, exp}}$, which ranged from 0.619 to 0.711 across strata defined by sex and age. As detailed in the Statistical Appendix, we used plausible values for other component terms in the bias factor (p_{smoker}, nonexp = 0.300; RR_{smoke} = 21.3 for males, 12.5 for females).[14,15] We also considered several extreme values for $p_{\text{smoker, exp}}$ and RR_{smoke} to test the robustness of our conclusions regarding the smoking-adjusted SIRs.

RESULTS

Cohort Description and Lung Cancer Incidence

We studied 5,238 HIV-infected patients treated at the Moore Clinic from 1989 to 2003. Approximately 300 to 500 patients entered the clinic each year, except for the first year (1989; n = 157) and the last year (2003; n = 83). Of these individuals, 3,605 (68.8%) were male, and the median age at entry was 37 years (range, 18 to 84 years; interquartile range, 32 to 43 years). Most were African American (n = 3,986; 76.1%), while the remainder were white (n = 1,155; 22.1%) or of other race (n = 97; 1.9%). By HIV-risk group, 2,183 (41.7%) were injection drug users, 1,266 (24.2%) were men who have sex with men, 238 (4.5%) had both risk factors, and 1,551 (29.6%) had other or unknown risk factors. At entry, the median CD4 count was 260 cells/mm^3 (interquartile range 72 to 462), and the median HIV viral load was 24,000 copies/mL (interquartile range, 1,670 to 112,000, based on 4,021 observations).

During 19,061 person-years of follow-up, 33 lung cancer cases were identified. Most patients (n = 22, 67%) were male, and the median age at diagnosis was 46 years (interquartile range, 41 to 53 years). Among lung cancer patients, 28 (85%) were current smokers, four (12%) were former smokers, and one (3%) had never smoked. For current smokers, the median pack-years of smoking at the time of cancer diagnosis was 37 (range, 5 pack-years to 80 pack-years). The most common histologic type of cancer was adenocarcinoma (n = 16, 48%), while the remaining cases were classified as squamous cell (n = 8, 24%), large-cell/anaplastic (n = 1, 3%), small-cell (n = 2, 6%), or other/unspecified carcinoma (n = 6, 18%).

Overall lung cancer incidence was 170 per 100,000 person-years. Lung cancer incidence increased with age ($P < .0001$) but did not vary significantly by sex, race, or injection drug user status (Table 1). There were no lung cancer cases before 1993, followed by a sharp increase from 1993 to 1995, and suggestion of a plateau in incidence thereafter. As a result, lung cancer incidence differed significantly across the three calendar periods selected before analysis (Table 1). Also, lung cancer incidence was higher, albeit not statistically significantly higher, in persons on HAART than not on HAART ($P = .10$), and was inversely related to HIV viral load ($P = .03$, Table 1). Lung cancer incidence was similar across strata defined by recent and nadir CD4 count.

In a multivariate model that considered age and calendar year together, age remained a strong predictor of lung cancer

Table 1. Incidence and Unadjusted Standardized Incidence Ratios for Lung Cancer in 5,238 Patients Infected With HIV, Moore Clinic, Johns Hopkins Hospital, Baltimore, MD

Characteristic	Lung cancers (No.)	Incidence (per 100,000 person-years)	P*	SIR v Detroit General Population		P*
				SIR	95% CI	
Total	33	170	—	4.7	3.2 to 6.5	—
Sex			.96			.02
Male	22	170		3.8	2.4 to 5.7	
Female	11	170		8.8	4.4 to 16	
Race			.27			.83
African American	28	190		4.7	3.1 to 6.8	
White/other	5	110		4.3	1.4 to 10	
Age, years			< .0001			.02
< 40	4	40		8.7	2.4 to 22	
40-49	17	240		6.6	3.8 to 11	
50+	12	560		3.0	1.5 to 5.2	
Calendar year range			.02			.20
1989-1994	2	60		1.7	0.2 to 6.3	
1995-1999	14	180		5.2	2.8 to 8.7	
2000-2003	17	220		5.3	3.1 to 8.4	
Injection drug use			.36			.41
No	14	150		4.0	2.2 to 6.7	
Yes	19	200		5.3	3.2 to 8.3	
HAART use†			.10			.42
No	12	140		4.2	2.2 to 7.4	
Yes	16	270		5.7	3.3 to 9.3	
Recent CD4 count, cells/mm^3			.54			.80
Missing	8	110		3.4	1.5 to 6.7	
0-49	4	270		8.9	2.4 to 23	
50-99	1	130		3.1	0.1 to 17	
100-199	3	190		4.5	0.9 to 13	
200-499	9	180		4.4	2.0 to 8.3	
500+	8	270		6.5	2.8 to 13	
Nadir CD4 count, cells/mm^3			.99			.54
Missing	0	0		0	0 to 75	
0-49	9	210		6.0	2.7 to 11	
50-99	4	240		5.3	1.5 to 14	
100-199	4	130		3.1	0.8 to 7.9	
200-499	12	170		4.5	2.3 to 7.9	
500+	4	150		4.8	1.3 to 12	
Recent HIV viral load, copies/mL			.03			.11
Missing	14	140		4.2	2.3 to 7.1	
< 400	12	360		6.9	3.6 to 12	
400-4,999	3	220		5.0	1.0 to 15	
5,000-49,999	2	100		2.6	0.3 to 9.4	
50,000+	2	100		3.0	0.4 to 11	

Abbreviations: SIR, standardized incidence ratio; HAART, highly active antiretroviral therapy.
*P values are for differences in incidence (using negative binomial regression models) or in standardized incidence ratios (using Poisson regression models). All P values are for tests of heterogeneity across categories, except P values for age, recent CD4 count, nadir CD4 count, and HIV viral load, which are based on tests for trend, excluding subjects with missing values.
†HAART use was analyzed for 1996-2003 calendar year range.

incidence (RRs, 5.6 [95% CI, 2.0 to 16] and 13 [95% CI, 4.3 to 38] for ages 40 to 49 and 50+ years, respectively, *v* age < 40 years), but calendar year was no longer significant ($P = .19$). Similarly, after adjustment for age, associations of lung cancer with HAART and HIV viral load were not significant ($P = .28$ and $P = .09$, respectively).

Comparison of Lung Cancer Incidence in the HIV-Infected Cohort and General Population

Overall, Moore Clinic patients were at substantially increased risk of lung cancer compared with the general population of the United States (SIR, 6.9; 95% CI, 4.8 to 9.7) and specifically of Detroit, an urban center similar to Baltimore (SIR, 4.7; 95% CI, 3.2 to 6.5). As presented in Table 1 for comparisons with Detroit, SIRs were generally elevated regardless of demographics, HAART use, CD4 count, or HIV viral load. Notably, although lung cancer incidence was similar in males and females, the SIR was more than two-fold higher in women than men ($P = .02$). Also, although incidence increased with age, the SIRs actually declined with age ($P = .02$), indicating that the excess risk in Moore Clinic patients was greatest at young ages (Table 1). SIRs did not vary significantly across other subgroups (Table 1).

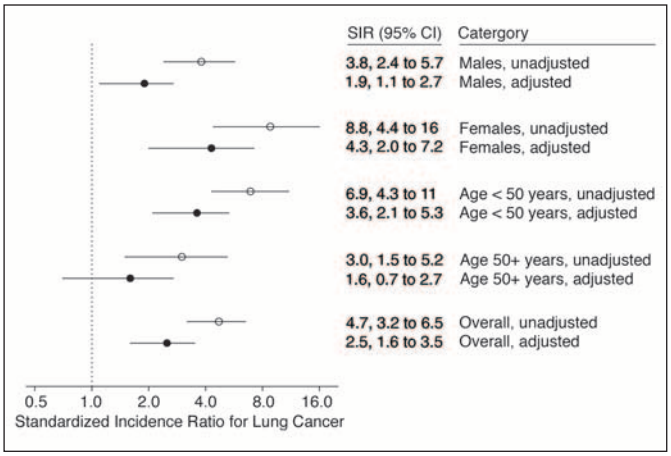

Fig 1. Standardized incidence ratios (SIRs) for lung cancer among HIV-infected patients, relative to the Detroit, MI, general population. SIRs are shown overall and separately by sex and age, and are presented unadjusted and adjusted for smoking using an indirect method described in the Statistical Appendix. Points depict SIRs, while horizontal lines show 95% CIs.

SIRs for subtypes of lung cancer were imprecise because there were few cases. Compared with the Detroit general population, SIRs were 6.4 (95% CI, 3.6 to 10) for adenocarcinoma, 5.4 (95% CI, 2.3 to 11) for squamous cell carcinoma, 1.5 (95% CI, 0.0 to 8.2) for large-cell/anaplastic carcinoma, 2.7 (95% CI, 0.3 to 9.8) for small-cell carcinoma, and 4.4 (95% CI, 1.6 to 9.6) for other/unspecified carcinoma.

Indirect Adjustment of Risk Estimates for Smoking

Among the 1,750 patients entering the Moore Clinic beginning in 1999, 69% were current smokers. Among smokers, 31% smoked one half pack per day or less, 41% smoked one pack per day, 17% smoked between one and two packs per day, and 11% smoked at least two packs per day. By comparison, in the general population of adults ages 25 to 54 years, 23% in the state of Maryland and 30% in the state of Michigan are current smokers.[14]

As described in the Statistical Appendix, we used an indirect method to adjust SIR estimates for the effect of smoking. Overall, the smoking-adjusted SIR was 2.5 (95% CI, 1.6 to 3.5) compared with Detroit. Smoking-adjusted SIRs are shown for men and women, and by age (Fig 1). Smoking-adjusted SIRs were roughly half of unadjusted SIRs, but were significantly different from the null value of 1.0, both overall and in all subgroups, except older individuals (age, 50+ years). After adjustment for smoking, the excess risk for lung cancer remained higher in women than men (ratio of smoking-adjusted SIRs, 2.3; 95% CI, 1.0 to 4.9) and higher in younger than older patients (ratio of smoking-adjusted SIRs, 2.3; 95% CI, 1.1 to 5.3), though these differences were marginally significant.

We also considered extreme scenarios to determine the degree to which smoking might plausibly account for the observed overall SIR of 4.7. If all of the Moore Clinic cohort patients were smokers ($p_{\text{smoker, exp}} = 1$), the smoking-adjusted SIR would still be 1.7. Alternatively, using the baseline values for $p_{\text{smoker, exp}}$, we calculated that doubling RR_{smoke}, the effect of smoking, would minimally change the smoking-adjusted SIR, to a value of 2.4.

DISCUSSION

We found a substantially increased incidence of lung cancer in HIV-infected individuals receiving medical care in an urban clinic—remarkably, almost seven times that seen in the general US population. When we compared our subjects to individuals in the general population of Detroit, an urban area like Baltimore and a region with the highest incidence of lung cancer among major SEER registries, lung cancer incidence was still markedly elevated (SIR, 4.7). Although some studies have observed little or no increase in lung cancer among HIV-infected persons,[16-18] our results are consistent with risk estimates in most prior reports (SIRs, 3 to 8).[1,3-6,8,9] Lung cancer incidence was elevated across all demographic subgroups, although younger adults and women seemed disproportionately affected (Fig 1).

Several lines of reasoning suggest that tobacco smoking accounts for much of this excess risk. First, smoking was 2 to 3 times as common in our cohort as in the Maryland and Michigan populations, and 97% of cases arose in current or former smokers. Second, incidence was elevated for most histologic types of lung cancer. Tobacco smoke contains over 60 known carcinogens,[19] and tobacco use has been linked to lung cancers of all subtypes.[20] Third, we found no evidence that lung cancer risk was associated with measures of immunosuppression, namely, recent and nadir CD4 counts. One prior study found that lung cancer incidence increased with advancing immunosuppression, as measured by time relative to AIDS onset,[1] but others did not find a relationship between lung cancer incidence and either time relative to AIDS onset or CD4 count.[7-9]

On the other hand, it is difficult to conclude that tobacco smoking was entirely responsible for the excess risk for lung cancer in our cohort. Our patients had smoked only a median of 37 pack-years at the time of diagnosis (ν 50 pack-years for other lung cancer patients treated in the Kimmel Cancer Center; author's unpublished analyses from the Sidney Kimmel Comprehensive Cancer Center database), suggesting a heightened susceptibility to the effects of smoking. Furthermore, almost half of our patients had adenocarcinomas. A large proportion of adenocarcinomas has been noted in some prior studies of lung cancer in HIV-infected individuals,[1,3,21,22] but not in other studies.[6,8] This observation is of interest because the association between tobacco use and lung adenocarcinoma is weaker than for other histologic types.[20] Conversely, only 6% of our lung cancers were small-cell carcinomas, even though this type is strongly linked with smoking.[20]

From an epidemiologic perspective, our analyses adjusting for the effects of tobacco use also indicated that smoking might not explain all of the lung cancer risk: after adjustment, the overall SIR remained elevated (2.5, 95% CI, 1.6 to 3.5, compared with Detroit's general population). We used an indirect method to adjust for the effects of smoking because we did not have data on tobacco use for the entire cohort. The high prevalence of smoking in our cohort inflated the SIRs by a bias factor on the order of 2.0 (Fig 1). Dividing by this bias factor as a method of indirect adjustment of the SIR has a long history.[23] Our study made use of new methods for incorporating uncertainty in the various components of the bias factor (see Statistical Appendix).[13] Even under implausible scenarios (ie, assuming all Moore Clinic cohort patients were smokers, or that the effect of smoking on lung cancer was twice as high as available data

suggest), we found that smoking would not wholly account for the elevated risk.

If a high prevalence of smoking does not entirely explain the excess risk of lung cancer in HIV-infected persons, what other mechanisms could be postulated? First, patterns of tobacco use could differ in ways that increase cancer risk in HIV-infected individuals. Although the limited data for smokers in our cohort did not indicate that smoking was unusually heavy, there is insufficient information to fully assess this possibility. Likewise, people with HIV infection could start smoking earlier in life, which would increase lung cancer risk.[24] Illicit drug use could promote cancer by inducing chronic lung damage,[25,26] but we did not find injection drug users to be at significantly higher risk than nonusers.

Another possibility is that the effects of HIV could interact with tobacco use to increase lung cancer risk. For instance, HIV infection is associated with an expansion of the pool of pulmonary macrophages and abnormally high levels in the lung of proinflammatory cytokines, such as interleukin-1, tumor necrosis factor, and interferon gamma.[27] Elevated levels of lysozyme and the chemokine RANTES detected in bronchoalveolar fluid could indicate an inflamed lower respiratory tract,[28] which might amplify the effects of tobacco carcinogens.[29] HIV-infected individuals have lower levels of antioxidant vitamins and minerals than HIV-uninfected controls[30] and manifest decreased lung levels of glutathione,[31] which could further predispose to tobacco-induced damage.

Finally, lung cancer incidence may be increased due to an unknown cofactor for lung cancer among persons with HIV infection. Some evidence points to specific infectious agents in lung cancer,[32-34] and HIV-induced immune dysregulation could amplify the effects of these or other microbes. Scars due to pulmonary infections might also be relevant.[35] We note that the elevation in risk appeared most pronounced for women, raising the possibility that a lung cancer risk factor could be more common or exert a greater effect in women.

We did not find strong evidence that HAART itself affects lung cancer risk. The apparent rise in incidence in our cohort over calendar time likely reflected aging, since this rise was attenuated after statistical adjustment for age. Likewise, the marginally elevated incidence of lung cancer seen in individuals on HAART and the trend of increasing incidence with lower HIV viral loads (Table 1) were largely due to confounding by age. One prior study found an increase in lung cancer incidence during the HAART era,[21] but others indicated no change in incidence with use of HAART or during the HAART era.[6,9,17]

Our study had several strengths. Our cohort is one of the largest for which data on lung cancer incidence have been analyzed, and the number of patients exceeded those in some prior cohort studies.[3-5,21] The setting in an urban clinic provided a representative picture of the HIV epidemic in US inner cities and yielded data on cancer risk in demographic subgroups (eg, African Americans, injection drug users) who continue to be disproportionately represented in the epidemic. Data on HAART use and HIV disease markers allowed us to examine risk related to these factors. A weakness of our study was that we did not have data on tobacco use for the entire cohort. Thus, we could neither directly measure the effect of smoking on lung cancer risk nor test for interactions with HIV-induced immunosuppression. Also, we lacked data on lung cancer incidence for the general population of Baltimore. Our use of Detroit SEER data seemed appropriate, however, because Detroit resembles Baltimore as a medium-sized city with a dense urban core. Finally, although we tried to identify all lung cancer cases, we may have underestimated lung cancer incidence if Moore Clinic patients received outside care or moved away.

In conclusion, we noted an elevated incidence of lung cancer among HIV-infected persons. As people with HIV infection live longer and age, lung cancer will likely grow in importance as a cause of morbidity and mortality. Clinicians should be alert to the possible diagnosis of lung cancer in HIV-infected patients. The high prevalence of tobacco use underscores the need to develop effective interventions to assist individuals in their attempts to quit smoking. Our observations also suggest that smoking might not entirely explain the excess of lung cancer among HIV-infected persons, pointing to a need for research regarding pathogenesis of lung cancer in this setting.

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Statistical Appendix and Table

The Statistical Appendix and Table are included in the full-text version of this article, available online at www.jco.org. They are not included in the PDF (via Adobe® Acrobat Reader®) version.

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The authors indicated no potential conflicts of interest.

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